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The MCD Spectra of Some 8-Azapurines*

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The magnetic circular dichroism spectra of 9-methyl-8-azapurine and of 7-, 8-, and 9-methyl-8-azaadenine have been found to be well resolved; as many as four distinct electronic bands are observable in the 200–350 nm spectral region. CNDO calculations indicate that $\pi \rightarrow \pi^*$ excitations are responsible for almost all of the MCD intensity. A comparison of four different parameterizations shows that a modification of Del Bene and Jaffé's CNDO/S procedure correctly predicts, with one exception, the sign of the observed *B*-terms and is therefore the most satisfactory method.

Key words: Magnetic circular dichroism spectra – Azapurine – Azaadenine

1. Introduction

Magnetic circular dichroism (MCD) spectroscopy is a sensitive method for the investigation of the electronic properties of nucleic acid bases [1–4]; it often resolves electronic bands which overlap in ordinary absorption spectra, so that experimental results and quantum mechanical SCF calculations may readily be compared.

We recently [4] reported a CNDO study of 7- and 9-methyl-adenine, and found that Del Bene and Jaffé's CNDO/S orbitals [5–8] were not entirely satisfactory for the description of the MCD spectra of these molecules. A slight modification of the CNDO/S method, however, was successful in predicting both the separation of the bands and the sign of the *B* terms.

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We now present the results of a similar investigation on some 8-azapurines, namely 9-methyl-8-azapurine (**1**), and 7-, 8- and 9-methyl-8-azaadenine (**2, 3, 4**). These recently described compounds are of particular interest because of their important biological properties [9].

2. Experimental

The MCD spectra were run on a Jasco Model ORD-UV 5 spectropolarimeter, modified for MCD measurements and equipped with a superconducting magnet (Model OSCM 103, Lockheed Palo Alto Research Laboratories). The spectra were measured in distilled water (pH = 7) at 20°C. The samples were a gift from A. Albert [9] and were used as received.

The B values were obtained by planimeter integration of the experimental curves, using the approximate formula

$$B = \frac{-1}{33.53\,\lambda_{\max}} \int [\theta]_M \, d\lambda$$

where $[\theta]_M$ is in units of deg cm^2 dmol^{-1} G^{-1}. When positive and negative B terms overlapped in the spectra the baseline was taken as the boundary and no attempt was made to correct for overlap; when B terms of the same sign overlapped we estimated the correction for overlap by extrapolation.

3. Theoretical Calculations

The MCD spectra were calculated by the procedure previously described [4]. The computations were based on molecular orbitals similar to those obtained by Del Bene and Jaffé's CNDO/S approximations [5–8]; the two-center repulsion integrals were calculated according to the Nishimoto-Mataga [10] formula, which yielded better results in previous studies [11]. Two different sets of parameters were introduced, the first being those used in the original CNDO/S procedure [5–8], the second the more recent set published by Jaffé and co-workers [12, 13]. In this paper the results corresponding to these different parameters are labelled CNDO/S and NCNDO/S respectively.

In our previous study [4] we obtained better results when we decreased the σ electron and increased the π electron delocalization. This was done by setting the scaling factor κ (which reduces the π overlap in the CNDO/S procedure) back to unity, as it is in CNDO/2, and by introducing an arbitrary parameter κ' to scale down the energies. The same procedure was applied in the present work with the same value of the scaling factor ($\kappa' = 0.65$); results obtained in this way are labelled CNDO/S′ (where the original set of parameters is used) and NCNDO/S′ (where the newer ones are introduced).

Origin dependence of the calculated B-values was checked on one of the compounds (9-methyl-8-azapurine, **1**). The origin, usually placed in the middle of the C(4)–C(5) bond (taken as y-axis), was moved by 1 Å along the x-axis, or by 1 Å along the y-axis, or to the center of the electric charges. These shifts resulted in variations of only

5–10 % in the *B* values, much smaller than the changes produced by modifying the CNDO parameterization. The error due to origin dependence was therefore neglected.

The crystallographic structures of both purine [14] and adenine [15] are well known, but no experimental geometries of either 8-azapurine or 8-azaadenine have been published. 8-azaguanine and 8-azahypoxanthine derivatives, however, have been studied repeatedly [16–21] and may be compared with guanine [15] and hypoxanthine [22]. Although replacement of the C–H group at position 8 of the purine skeleton by an N atom does somewhat affect the geometry of the molecule [23], the changes involved are usually small (a few hundredths of an Ångstrom at most) and may probably be neglected in CNDO calculations (care should be taken not to relate protonated or methylated sites with unprotonated or unmethylated ones, when comparing different molecules). We carried out computations with two different types of geometries: the first were the geometries of purine and adenine in which C(8)–H was replaced by N(8) with no change of coordinates; the second were combinations between the geometries of purine or adenine for the six-membered ring and that of 8-azaguanine [17, 18] for the triazole ring. Only few significant differences were seen between the two sets of calculations; these will be discussed below. The results presented here were obtained with the second type of geometries.

4. Results and Discussion

The experimental MCD and absorption spectra are presented in Figs. 1–4. The MCD spectra of 7-methyl- and 9-methyl-8-azaadenine (**2, 4**) are qualitatively similar to those of 7-methyl- and 9-methyl-adenine [4]; both show four separate bands above 200 nm, with the same sign pattern ($-+--$) (long wavelength bands first) but with somewhat reduced intensities in the longest wavelength bands. The MCD spectrum of 8-methyl-8-azaadenine (**3**) also shows four bands, with a ($+--+$) sign pattern, while 9-methyl-8-azapurine (**1**) has only two bands above 200 nm with ($+-$) signs and relatively high intensities. In contrast, the absorption spectra are much less detailed; a single absorption band appears above 200 nm for **1**, and each of the azaadenines shows only two such bands. Because of this lack of resolution the discussion will be centered mainly on the MCD spectra.

The results may be qualitatively interpreted in the light of some previous studies on the MCD spectra of substituted benzenes. Foss and McCarville [24] first noted that the sign and intensity of the long wavelength band in substituted benzenes was directly related to the Hammet σ_{para} function for the substituent. This observation was studied in more detail by Seamans [25], Shieh *et al.* [26, 27], Teramae *et al.* [28], and Michl *et al.* [29, 30]. Shieh *et al.* [27], in particular, noted that the *B* value of the $^1A_{1g} \rightarrow {}^1B_{2u}$ excitation in parasubstituted benzenes is linearly related to the resonance contribution to the Hammet constant of the substituent. Michl and Michl [29] performed explicit calculations on similar compounds and found that mesomeric effects far outweigh inductive ones. It therefore appears that if we assume purines to be substituted pyrimidines and the main property of the substituents to be their π donor or acceptor strength, we may compare the MCD spectra of azapurines

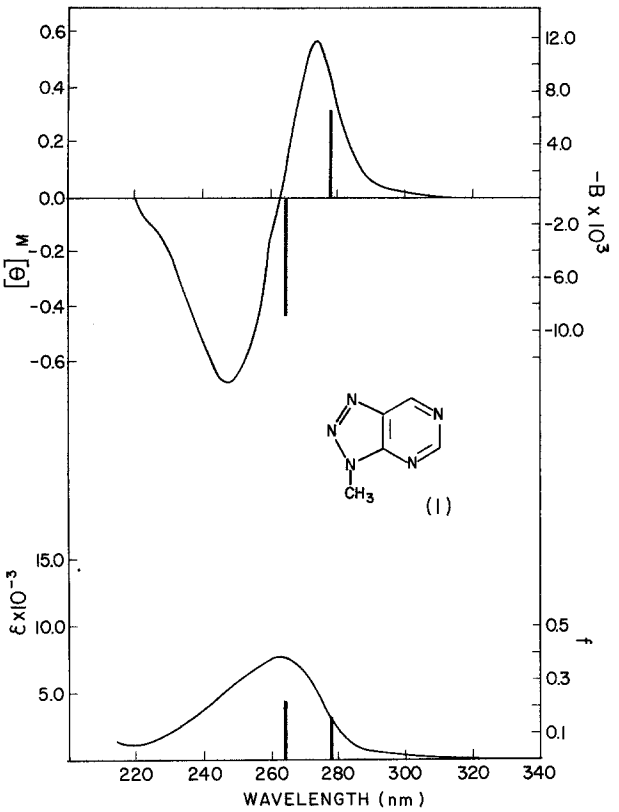

Fig. 1. MCD and absorption spectra of 9-methyl-8-azapurine (**1**). The $-B$ and f values obtained by CNDO/S′ are indicated by bars

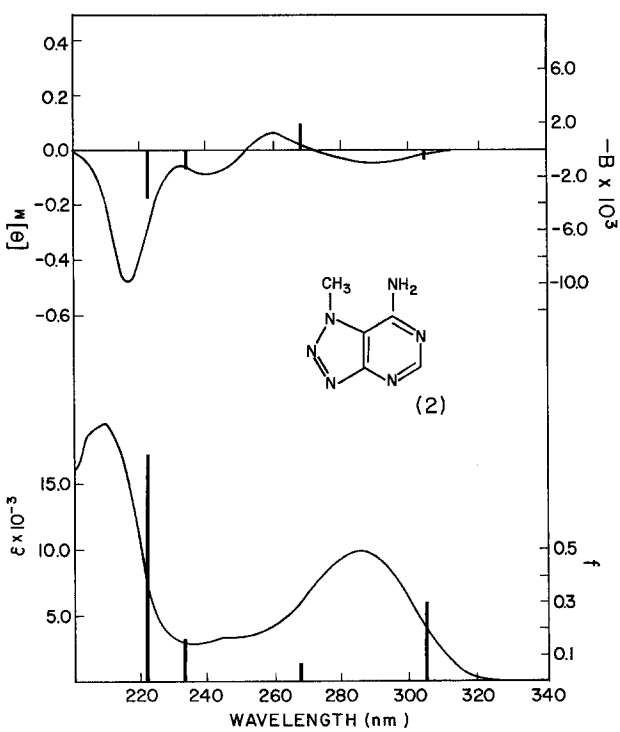

Fig. 2. MCD and absorption spectra of 7-methyl-8-azaadenine (**2**). The $-B$ and f values obtained by CNDO/S′ are indicated by bars

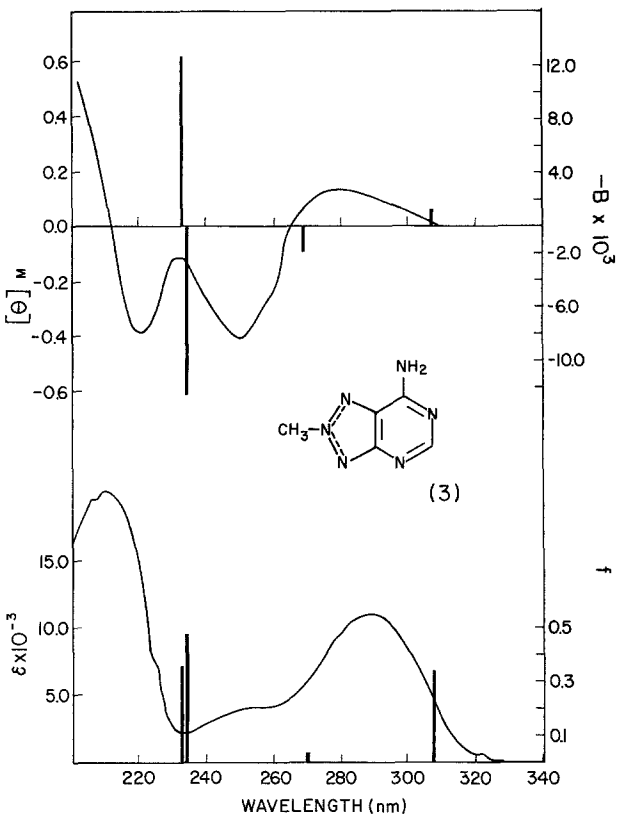

Fig. 3. MCD and absorption spectra of 8-methyl-8-azaadenine (**3**). The $-B$ and f values obtained by CNDO/S′ are indicated by bars

with each other and with those of other purines in the following way. First the B value of the long wavelength band in 7-methyl- and 9-methyl-8-azaadenine (**2, 4**) is much lower than that of the corresponding 7-methyl- and 9-methyl-adenine [4], in keeping with the electron withdrawing power of the 8-aza nitrogen. Then the sign of this band is reversed in 8-methyl-8-azaadenine (**2**) with respect to the 7- and 9-methyl compounds, though the intensity remains weak; this is probably the result of converting both N(7) and N(9) into π-accepting, pyridine-type, nitrogens. The trend is continued if we move from a dominance of electron donating substituents in the adenines to the converse: removal of the 6-amino group results in a strongly increased negative B value for the long wavelength band of 9-methyl-8-azapurine (**1**). Fig. 5 gives the π-charge distribution we obtained by CNDO/S and CNDO/S′ calculations for the series.

5. CNDO Results

As already mentioned, we performed CNDO calculations of the MCD spectra of the azapurine derivatives in four approximations, two (CNDO/S and NCNDO/S) using the two sets of parameters which Jaffé and co-corkers have published [5–8, 12, 13], and the two others (CNDO/S′ and NCNDO/S′) being a modification [4] of

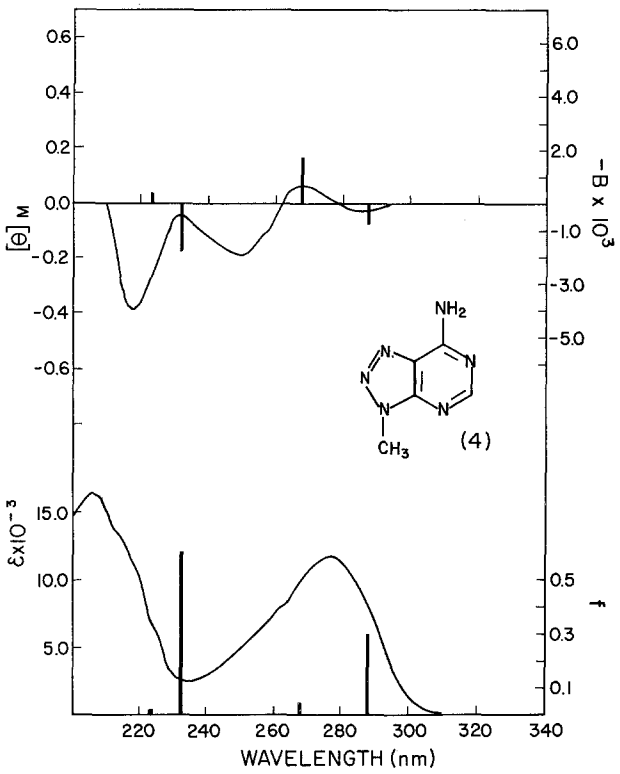

Fig. 4. MCD and absorption spectra of 9-methyl-8-azaadenine (**4**). The $-B$ and f values obtained by CNDO/S′ are indicated by bars

their method. The results of these computations are presented in Table 1; the signs of $-B$ for the experimental and calculated bands are summarized in Table 2.

It can be seen immediately that only the CNDO/S′ approximation (our variation with Del Bene and Jaffé's original parameters) consistently gives the correct sign for the two longest wavelength bands. The three other approximations yield correct signs of B for the two first bands of 9-methyl-8-azapurine (**1**) and 8-methyl-8-azaadenine (**3**), but not for the first two bands of 7-methyl- and 9-methyl-8-azaadenine (**2, 4**).

If we consider the shorter wavelength bands of the spectra, we see that the CNDO/S′ results are of the correct sign for bands III and IV of **2** and **3** and for band III of **4**; band IV of the last compound, however, is of the wrong sign and this sign depends on the precise geometry used for the computation (Table 1).

The sensitivity of the results of the methylated 8-azaadenine series to the precise CNDO parameterization reflects the fact that the experimental MCD amplitudes are quite small in these compounds. It is all the more gratifying that only one band, out of the fourteen experimental ones studied, is not entirely correctly computed by the CNDO/S′ approximation, a fact which increases our confidence in the method. For a closer comparison between calculated and experimental results, the $-B$ values and oscillator strengths obtained by the CNDO/S′ method have been added

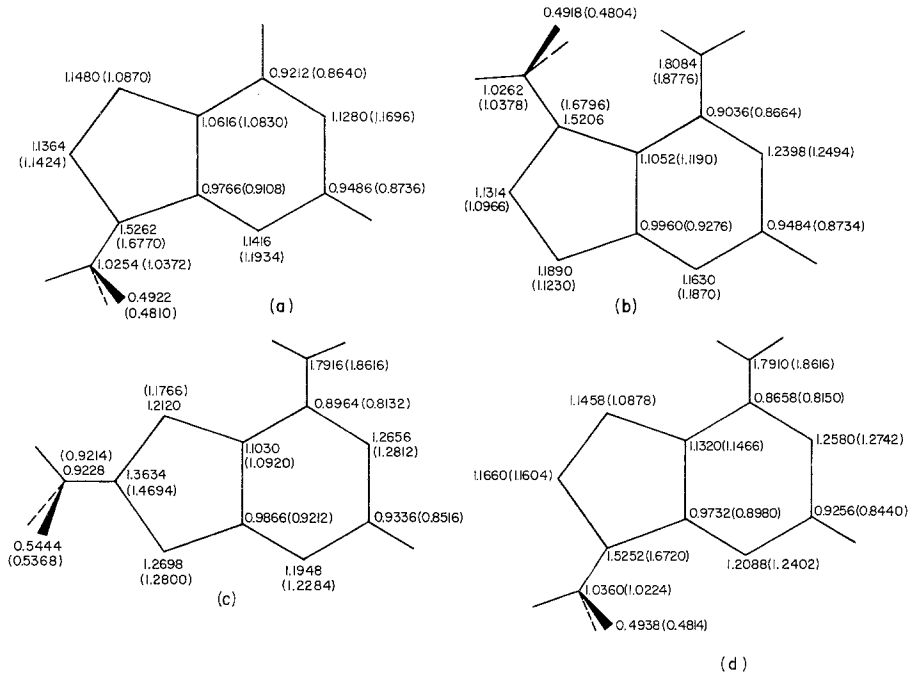

Fig. 5. The π-charge distribution obtained by CNDO/S′ (and in brackets, by CNDO/S) for a) 9-methyl-8-azapurine (**1**), b) 7-methyl-8-azaadenine (**2**), c) 8-methyl-8-azaadenine (**3**), and d) 9-methyl-8-azaadenine (**4**)

as bars to Figs. 1–4. The relative positions and intensities are well reproduced for 9-methyl-8-azapurine (**1**) (Fig. 1) and 7-methyl-8-azaadenine (**2**) (Fig. 2). Once allowance is made for the calculated near degeneracy ($\Delta\lambda = 0.8$ nm) of bands III and IV of 8-methyl-8-azaadenine (**3**) (Fig. 3) and for the concomitant exaggeration of the calculated $-B$ values, the agreement is satisfactory too. Even in the case of 9-methyl-8-azaadenine (**4**) (Fig. 4), where bands III and IV appear to be interchanged, the relative intensities of all but band IV are reasonable.

In the preceding calculations configuration interaction of the $\pi \rightarrow \pi^*$ transitions only were taken into account. To check the validity of this restriction a few more extensive computations were made. These introduced, in addition to all π and π^* levels, several of the σ and σ^* levels; they were carried out for the slightly simpler, but electronically almost identical, unmethylated 8-azapurine (N(9)–H tautomer) and 8-azaadenine (N(7)–H, N(8)–H and N(9)–H tautomers). All previously found $\pi \rightarrow \pi^*$ bands were essentially unaffected by the introduction of the wider configuration interaction. Some $\sigma \rightarrow \pi^*$ bands did appear above 200 nm, but were so weak as to be negligible (B is usually less than 10^{-5} in absolute value). One exception was 8-azapurine, for which a relatively large $\sigma \rightarrow \pi^*$ band is predicted at 295 nm ($B = 0.149 \cdot 10^{-3}$); but even this band is smaller by an order of magnitude than the neighboring $\pi \rightarrow \pi^*$ band and it is doubtful whether it could be resolved

Table 1. Experimental and calculated spectral parameters[a]

	Experimental			CNDO/S			NCNDO/S			CNDO/S′			NCNDO/S′		
Band[b]	$-B\cdot10^3$	f	λ_{max}	$-B\cdot10^3$	f	λ_{max}	$-B\cdot10^3$	f	λ_{max}	$-B\cdot10^3$	f	λ_{max}	$-B\cdot10^3$	f	λ_{max}
	A. 9-methyl-8-azapurine (**1**)														
I	0.927		274	1.576	0.107	276	0.964	0.257	266	6.488	0.159	278	16.926	0.157	266
		0.185	262												
II	−1.904		247	−2.264	0.251	250	−0.645[d]	0.224	240	−8.854	0.222	264	−19.528	0.328	260
	B. 7-methyl-8-azaadenine (**2**)														
I	−0.105		291	0.812	0.167	295	0.785	0.257	293	−0.651	0.301	305	0.181[d]	0.318	299
		0.217	285												
II	0.085		259	−1.162	0.064	247	−1.180	0.041	234	1.947	0.065	268	0.623	0.028	253
III	−0.182		242	0.849	0.061	223	−0.112	0.001	218	−1.139	0.171	234	−1.068	0.211	228
IV	−0.908		216	−1.733	0.836	214	0.089	0.883	205	−3.435	0.848	222	−1.284	0.830	217
		0.578	209												
	C. 8-methyl-8-azaadenine (**3**)														
I		0.255	290												
	0.390		280	3.359	0.261	293	2.654	0.294	288	1.137	0.354	307	1.803	0.367	299
II	−1.014		250	−4.298	0.083	271	−3.707	0.127	256	−1.864	0.027	268	−3.110	0.093	260
III	−0.812		219	−0.678	0.045	223	−0.901	0.177	213	−12.562	0.487	233	−6.581	0.736	226
		0.642	210												
IV	>0[c]			0.692	0.557	216	0.795	0.444	204	12.704	0.363	232	7.589	0.074	224
	D. 9-methyl-8-azaadenine (**4**)														
I	−0.0387		285	0.895	0.004	275	0.535[d]	0.154	260	−0.755	0.305	287	0.712	0.338	274
		0.241	277												
II	0.0806		270	−0.960	0.310	259	−0.090[d]	0.253	250	1.172	0.046	267	−0.892	0.037	258
III	−0.459		250	−0.179	0.449	218	−1.014	0.318	211	−1.791	0.606	232	−0.911	0.606	225
IV	−0.757		217	−3.095	0.467	204	0.398	0.344	197	0.351[d]	0.010	223	0.526	0.021	215
		0.503	205												

[a] B values are in bohr magneton debye^2/wavenumber units, wavelengths are in nanometers.

[b] For band identification see Figs. 1–4.

[c] Only a small portion of this band can be determined experimentally (see Fig. 3).

[d] This calculated band changed sign when the geometry of the molecule was modified (for geometries, see Sect. 3).

Table 2. Predicted and experimental signs of the MCD bands ($-B$)

Compound	Band[a]	CNDO/S	NCNDO/S	CNDO/S′	NCNDO/S′	Experimental
9-methyl-8-azapurine (**1**)	I	+	+	+	+	+
	II	−	−[b]	−	−	−
7-methyl-8-azaadenine (**2**)	I	+	+	−	+[b]	−
	II	−	−	+	+	+
	III	+	−	−	−	−
	IV	−	+	−	−	−
8-methyl-8-azaadenine (**3**)	I	+	+	+	+	+
	II	−	−	−	−	−
	III	−	−	−	−	−
	IV	+	+	+	+	+
9-methyl-8-azaadenine (**4**)	I	+	+[b]	−	+	−
	II	−	−[b]	+	−	+
	III	−	−	−	−	−
	IV	−	+	+[b]	+	−

[a] For band identification see Figs. 1–4 and Table 1.

[b] The calculated sign of these bands changes when the geometry is modified (Sect. 3)

experimentally. It seems therefore that the introduction of only $\pi \rightarrow \pi^*$ transitions in the MCD computations is justified[1].

It should be noted that small modifications in the geometries which are used as input data for the CNDO calculations do not influence the results very much. Slight variations in the wavelengths and intensities of the calculated bands are usually observed, but except in borderline cases (where weak bands such as band IV of 9-methyl-8-azaadenine (**4**) may change their calculated sign when the geometry is altered) these variations do not affect the main trend of the results. It is nevertheless certain that additional experimental information on the molecular dimensions of these compounds would be useful.

6. Conclusion

Our results indicate that while the CNDO/S method is unable to predict the MCD spectra of the compounds studied here, the CNDO/S′ modification is almost totally satisfactory. This probably reflects the excessive σ-delocalization which the CNDO/S approximation introduces into aromatic molecules containing several heteroatoms or strong π-donor/acceptor substituents, while in the CNDO/S′ method the σ-delocalization has been reduced with regard to that of the π-electrons.

[1] No procedure has yet been established for properly handling $\sigma \rightarrow \pi^*$ excitations in the CNDO/S′ calculations. Since we wished to obtain only order of magnitude estimates for the $\sigma \rightarrow \pi^*$ excitations, we used the CNDO/S parameterization, in spite of its numerical drawbacks, to carry out these computations.

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